Use of Toxicokinetic Data to Replace Default Uncertainty Factors for the Derivation of a Reference Dose for Boron

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EPA Science Forum 2004
Healthy Communities and Ecosystems

Boron is on the Office of Water's Candidate Contaminant List, indicating the potential for regulatory consideration. The Office of Research and Development's (ORD) National Center for Environmental Assessment (NCEA) is charged with assessing risks from exposure to environmental contaminants, and developing and applying advanced risk assessment methods. The reassessment of boron's health risks presented a unique opportunity to develop and apply chemical-specific information in quantitative human health risk assessment. Chemicals are absorbed, distributed and eliminated from animals through toxicokinetic (TK) processes while toxicodynamic processes (TD) deal with the response of the target tissue to a given dose. For risk assessment, differences between animals and humans, and differences within humans are each addressed with a default uncertainty factor of 10, and can be divided into TK and TD components. The default value for each component can be replaced with data-derived values. Prior to initiating the boron risk assessment, no such data existed to evaluate TK differences between animals and humans, or TK differences within humans. Through a partnership with industry (US Borax), NCEA guided the planning, development, conduct, interpretation and presentation of studies to determine boron TK in pregnant rats and pregnant humans. Human studies were funded by US Borax, and conducted by the University of California at Irvine; results were published in the peer-reviewed literature. NCEA scientists used these data to develop a value to replace the default value for the TK component of animal to human extrapolation. NCEA scientists critically evaluated a diverse set of data on kidney function to determine how boron is removed from mammals, and used variability in renal function among humans to develop a value to replace the default value for the TK component of the interindividual uncertainty factor. This precedent-setting assessment demonstrates NCEA's adherence to reducing uncertainties in human health risk assessment, and our intent to include quantitative information, when possible, in Agency risk assessments. This interaction and its outcome highlights ORD's ability to partner with industry to fill data gaps and is important for enabling an improved scientific basis for risk assessment. This assessment, with its inclusion of data-derived uncertainty factors, will stimulate similar advances in the quantitative reliance on TK data when they are available for other chemicals. The Risk Assessment Forum is considering whether to guide the replacement of default uncertainty factors with data-derived uncertainty factors; this assessment will be useful as a case study in that decision.

boron

Boron is a naturally occurring element usually found as borates in nature.

Where is the Exposure to Boron?

Diet

Consumer Products

Manufacturing

Potential for Regulatory Consideration?

What is the risk?

Determination of the RfD Using Adjustment Factors

$$RfD = D_C / (AF_{AK} \cdot AF_{AD} \cdot AF_{HK} \cdot AF_{HD} \cdot UF)$$

where:

D_C is the "critical" dose (NOAEL, LOAEL, BMD) defined in the critical study,
AF_{AK} is the interspecies toxicokinetic adjustment factor (default = 3.16),
AF_{AD} is the interspecies toxicodynamic adjustment factor (default = 3.16),
AF_{HK} is the interindividual toxicokinetic adjustment factor (default = 3.16),
AF_{HD} is the interindividual toxicodynamic adjustment factor (default = 3.16),
UF is the aggregate uncertainty factor,

Research Protocols

What about Adjustment Factor Data to Replace Defaults

Through a partnership with industry (US Borax), NCEA guided the planning, development, conduct, interpretation and presentation of studies to determine boron TK in pregnant rats and pregnant humans.

NCEA scientists used these data to develop a value to replace the default value for the TK component of animal to human extrapolation

Uncertainty Factors for Boron Defaults or Data?

Default and Data-Derived Values for Components of UF_A and UF_H

Uncertainty Factor	Component		Combined Factor Values
	TD	TK*	
UF_A	(3.16) not replaced no data	(3.16) 3.3	10.43
UF_H	(3.16) not replaced no data	(3.16) 2.0	6.32
Combined UF_A and UF_H			66

*Valuation of the TK component of UF_A was based on species difference in the volume of total body water during pregnancy and boron clearance rates; valuation of the TK component of UF_H was based on differences in GFR among pregnant women.

Values Used for Boron Reference Dose

D_C = 10.3 mg/kg-day (Allen et al., 1996)

AF_{AK} = 3.3 (data-derived)

AF_{AD} = 3.16 ($10^{0.5}$, default)

AF_{HK} = 2.0 (data-derived)

AF_{HD} = 3.16 ($10^{0.5}$, default)

UF = 1 (UFS x UFD x UFL)

AF_{TOT} = 66 (3.3 x 2.0 x 3.16 x 3.16)

RfD = 0.2 mg/kg-day (10.3/66)

The RfD is consistent with a suggestion by Nielsen (1992) that an intake of 10 mg per day is not too high, while 50 mg/day is probably toxic. If a representative body weight of 60 kg is assumed for a pregnant woman, the value of 10 mg/day translates to 0.17 mg/kg-day. As boron appears to have some beneficial nutrient value, Nielsen (1992) also recommended a total daily boron intake of 1 mg to avoid boron deficiency. The RfD would appear to give an adequate margin of safety below, as well as above.

How we got there....

Critical Dose

- The critical dose for Boron was determined by using a Benchmark Dose (BMD) for decreased fetal body weight in rats (Allen et al. 1996) using combined data from two studies performed in the same laboratory. (Heindel et al., 1992; Price et al., 1996)
- The BMD based on the combined results of the two studies was 10.3 mg B/kg-day.

Interspecies Toxicokinetics

- As the boron RfD is based on developmental effects observed in rats, the most relevant kinetic data are those pertaining to pregnant rats and pregnant humans.
- Boron clearance is used as an estimator of internal dose.
- Boron is not metabolized and almost entirely eliminated in the urine, clearance of boron by the kidney can be used as the key toxicokinetic interspecies scaling factor therefore the TK component of UFA was based on species difference in boron clearance.
- There is an assumption of relatively constant intake of boron, and the toxic outcome is most likely related to a continuous exposure over an extended period during fetal development, the most appropriate estimator for internal dose is the average steady-state circulating boron concentration.
- Boron distributes primarily to total body water and bone, a two-compartment steady-state kinetic model is used to relate internal circulating boron concentration to external exposure.
- The mean boron clearance for pregnant rats and pregnant women were determined from the kinetic studies of U.S. Borax (2000), Vaziri et al. (2001) and Pahl et al. (2001).

Intraspecies Toxicokinetics

- (AFHK) accounts for the range of human interindividual variability from where AFAK left off to where the sensitive subpopulation is adequately protected.
- For boron, the range is between the mean and a "lower bound" boron clearance in the pregnant human population.
- The TK component of UFH for Boron was based on differences in GFR among pregnant women.

The basic formula modified from Dourson et al. (1998) for AFHK is:

$$AF_{HK} = GFR_{AVG} / (GFR_{AVG} - 3SD_{GFR})$$

where GFR_{AVG} and SD_{GFR} are the mean and standard deviation of the GFR (ml/min) for the general healthy population of pregnant women. The use of 3 standard deviations rather than 2 (as in Dourson et al., 1998) is based on obtaining adequate coverage of pregnant women with very low GFR.

Sigma Value Calculation

Study	Mean GFR (SD) (mL/min)	Mean GFR - 3SD mL/min	Sigma-Method Value[a]
Dunlop (1981)	150.5 (17.6)[b]	97.7	1.54
Krutzén et al. (1992)	195 (32)[c]	99	1.97
Sturgiss et al. (1996)	138.9 (26.1)[d]	60.6	2.29
Averages	161.5	85.8	1.93

[a] Mean GFR ÷ (Mean GFR - 3 SD)
[b] Serially-averaged observations across three time periods (16, 26, & 36 weeks) for 25 pregnant women
[c] 3rd trimester values for 13 pregnant women
[d] Serially-averaged observations across two time periods (early and late pregnancy) for 21 pregnant women (basal index plus basal control individuals)

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